Vol. 97 (2003) (SUPPLEMENT A), S9–S21

respiratoryMEDICINE

Early clinical investigation of Viozan™ (sibenadet HCl), a novel D_2 dopamine receptor, β_2-adrenoceptor agonist for the treatment of chronic obstructive pulmonary disease symptoms

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Abstract Viozan™, (Sibenadet HCl, AR-C68397AA) is a dual D_2 dopamine receptor, β_2-adrenoceptor agonist that combines bronchodilator activity with the sensory afferent modulating effects associated with D_2-receptor agonism. Investigation in animal models of key chronic obstructive pulmonary disease (COPD) symptoms has demonstrated that sibenadet effectively inhibits sensory nerve activity, thereby reducing reflex cough, mucus production and tachypnoea. The results of the early clinical evaluation of this novel agent are reported.

An initial proof of concept study (Study 1) aimed to determine the clinical potential of this novel agent by assessing the effects of three doses of sibenadet therapy relative to placebo, with two commonly used bronchodilators, intended to provide a benchmark against which sibenadet activity could be judged. In all, 701 patients were randomized to one of three sibenadet dose groups (400, 600 or 1000 μg *ex valve*), salbutamol 200 μg, ipratropium bromide (IB) 40 μg or placebo, all three times daily via pressurized metered dose inhaler (pMDI) for 4 weeks. Once the results of Study 1 had been evaluated, a dose-ranging, study (Study 2) involving 872 patients randomized to receive sibenadet (45, 270, or 495 μg *ex actuator*), or placebo all three times daily via pMDI, for 6 weeks commenced. Both studies were preceded by a 2-week baseline phase and followed by a 2-week follow up period. The primary efficacy variable identified changes in key COPD symptoms over the treatment period (compared with baseline data) as determined by the novel Breathlessness, Cough and Sputum Scale (BCSS©). In addition, data on lung function, health-related quality of life and adverse events were collected.

Patients receiving sibenadet therapy three times daily exhibited statistically significantly greater improvements in BCSS total score than those receiving placebo or bronchodilator therapy alone. A clear dose-response was evident in Study 2. Symptom improvement in this study was also accompanied by improved lung function and health-related quality of life. Sibenadet therapy was well tolerated with an adverse events profile comparable to current bronchodilator therapy. These data were viewed as extremely encouraging, warranting further, large-scale clinical investigation.

Keywords COPD; Viozan; sibenadet HCl; Breathlessness, Cough and Sputum Scale (BCSS); symptoms; ipratropium bromide; salbutamol; clinical study; daily diary card; patient-reported outcome measure.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) refers to a disease spectrum with slowly progressive, poorly reversible airways obstruction due to chronic bronchitis, emphysema, small airways disease or a combination of these conditions. The single greatest risk factor for the development of COPD is long-term tobacco smoking, which accounts for 80–90% of all cases (1). However, only around 15% of smokers go on to develop COPD. In non-smokers, COPD can be attributed to environmental pollution, occupational hazards and genetic abnormalities (2). Although many patients remain undiagnosed, the global prevalence is thought to be 4–6% in those over 45 years of age (2). The impact of COPD continues to

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intensify as the trend towards increased smoking in women continues (3). In addition, COPD is likely to become a particular problem in developing nations, where both life expectancy and cigarette smoking are increasing (4). Mortality projections reflect this situation, predicting that COPD will become the third leading cause of death worldwide by 2020 (5). The associated economic burden of COPD is considerable. In the U.S.A., the total healthcare expenditure for COPD is approximately twice that of asthma (6).

In contrast to asthma, the airflow obstruction experienced by patients with COPD is largely irreversible. The Global Initiative on Obstructive Lung Disease (GOLD) guidelines have identified breathlessness, cough and sputum as the key symptoms associated with COPD (7), the chronic nature of which results in progressive impairment of health-related quality of life (HRQL), limiting individual activity and social functioning (8–10). The mechanisms underlying these key symptoms are poorly understood, but reflex activation of sensory afferent nerves by irritants is known to induce bronchospasm, cough, and sputum production (10,11). This process normally acts as a protective mechanism to prevent contamination of the lung by irritant chemicals, dust or smoke, but in patients with COPD constant activation of sensory nerves in the airways may contribute to their symptoms. It has been shown that activation of D_2-receptors in the periphery can modulate neuronal activity, generally in an inhibitory manner (12) and dopamine can inhibit the discharge of rapidly adapting receptors in the dog lung (13). In addition, D_2-receptor mRNA has been demonstrated in the ganglia of sensory nerves associated with reflex pathways (14). The driving hypothesis for the development of new treatments was that stimulation of D_2-receptors present on sensory nerves in the lung could suppress reflex-mediated COPD symptoms (15).

Sibenadet HCl (Viozan™, AR-C68397AA) is a dual D_2 dopamine receptor, β_2-adrenoceptor agonist that combines the bronchodilator activity of a β_2-adrenoceptor agonist with the sensory afferent modulating effects associated with D_2-receptor agonism. Preclinical evaluation has shown sibenadet to have prolonged β_2-agonist duration of action, resulting in effective bronchodilator activity. The D_2-receptor agonist property has been shown to inhibit the response of sensory receptors to irritant stimuli in relevant animal models (16). In dog models driven by stimulation of sensory nerve activity, sibenadet has been shown to inhibit capsaicin-induced cough, histamine-induced tachypnoea, and reflex-induced mucus secretion (16). Cooling or cutting the vagus inhibited both the tachypnoea and mucus production responses, indicating their reflex origin. These effects of sibenadet were obtained in the presence of β-blockade and were reversed by pre-treatment with D_2-selective antagonists including the peripherally active antagonist domperidone. This suggests that they were mediated via dopamine D_2 receptors outside the central nervous system. This comprehensive evaluation provided convincing evidence of the mechanism of action of sibenadet and suggested important clinical potential.

The results of the early clinical evaluation of sibenadet are reported here. An initial 'proof of concept' study aimed to determine the clinical potential of this novel agent by comparing the effect on key COPD symptoms of a range of doses of sibenadet with that of placebo, and with common bronchodilator therapies (salbutamol or IB) included to provide a benchmark against which sibenadet activity could be judged. The results of this trial led to a second, dose-ranging, study to investigate the clinical efficacy and tolerability of sibenadet across a range of doses in comparison with placebo. These studies represent the first use of the novel Breathlessness, Cough and Sputum Scale (BCSS©), a unique patient-reported outcome tool designed to detect symptomatic changes in patients with COPD (17,18).

METHODS

Study design

The clinical evaluation reported here comprised two multicentre, double-blind, placebo-controlled studies. Study 1 was a 4-week 'proof of concept' study designed to investigate the clinical efficacy of sibenadet in patients with COPD, using bronchodilator therapy as a benchmark. This study was conducted in 69 centres in eight European countries and Canada. After clinic screening, patients entered a 2-week baseline period at the end of which eligible patients were randomized to one of three sibenadet dose groups (400, 600 or 1000 μg *ex valve*), salbutamol 200 μg, IB 40 μg or placebo all by pMDI three times daily for a total of 4 weeks. A follow-up visit took place 2 weeks after the end of the treatment period. As bronchodilators were included as controls rather than comparators, three times daily dosing of IB and salbutamol was considered sufficient to achieve the purpose of this study and a complex double dummy study design to enable a more conventional dosing frequency of four times daily was not adopted.

Study 2 was a 6-week dose-ranging study, conducted in 77 centres in Europe and 19 centres in the U.S.A. After completing a 2-week baseline period, eligible patients were randomized to receive sibenadet (45, 270, or 495 μg *ex actuator*), or placebo via pMDI, three times daily, for 6 weeks followed by a 2-week follow-up period. The three sibenadet doses were selected on the basis of the findings from Study 1. In both studies, patients were assessed at clinic visits on entry to the study, at the start of treatment, after 2 weeks' treatment, at the end of treatment and at the end of follow-up.

In both studies, patients were required to discontinue any routine inhaled long-acting bronchodilators during the baseline and treatment periods and short-acting bronchodilators during the treatment period. Other regular medications (corticosteroids, mucolytics and methylxanthines) could be continued providing a constant dose was maintained for the duration of the study. A short-acting inhaled β_2-agonist (salbutamol [Ventolin™, GlaxoSmithKline] pMDI, 100 μg per actuation, *ex valve*) was provided for use as rescue therapy. Throughout the study, patients were required to complete daily diary cards recording symptoms, morning and evening peak expiratory flow (PEF) measurements, rescue medication usage, changes in concomitant medication and any adverse events (AEs).

The studies were performed in accordance with the Declaration of Helsinki and approved by Ethics Committees at each centre. All patients gave written informed consent.

Patient population

Male and female patients between 45 and 75 years of age with stable, smoking-related COPD (smoking history of ≥ 15-pack-years) were eligible for inclusion in these studies if symptoms had persisted for ≥ 2 years. At screening, they were required to have a forced expiratory flow in one second (FEV_1) 20–70% of predicted normal and a FEV_1/FVC (forced vital capacity) ratio of < 65%. In Study 1, patients were additionally required to meet at least two of the following criteria: no atopy history; ≤ 15% reversibility, or an increase in FEV_1 of < 200 ml, after inhaled salbutamol (400 μg); prior evidence of diffusing capacity < 80% of predicted normal; previous evidence of emphysematous change on CT scan or X-ray, excluding over-inflation. In Study 2, an additional criterion was included to ensure qualifying patients were symptomatic; at the end of the baseline period, patients were required to have a mean daily BCSS total score of ≥ 2 over any 7 consecutive days to qualify for randomization.

Subjects were excluded if they had a history of a respiratory tract disorder other than COPD; onset of symptoms of chronic airways disease before the age of 35 years; reversibility in FEV_1 greater than 200 ml or 15% increase from baseline after inhalation of 400 μg salbutamol; significant exacerbation of COPD in the previous 6 weeks (defined as requiring prescription of antibiotics or a change in oral/inhaled corticosteroid and/or methylxanthine therapy or requiring hospitalization); if they required domiciliary oxygen; exhibited laboratory abnormalities considered to be clinically significant or used any disallowed medications (inhaled long-acting bronchodilators, anticholinergics, oral β-agonists, leukotriene antagonists, dopamine agonists or antagonists, β-adrenoceptor blockers, antibiotics for respiratory tract infections, or initiation of any antitussives, decongestants, mucolytics or proprietary medicines intended to reduce sputum production and/or cough).

Outcome measures

Primary efficacy variable

The primary efficacy variable for both studies was the change in BCSS total score from the mean over the baseline period to the mean over the treatment period. Changes from baseline to each week and each 2-week period within the treatment period were also examined in Studies 1 and 2 respectively. In Study 1 the planned primary comparisons were between the 1000 μg sibenadet dose and IB, salbutamol and placebo.

In Study 1, BCSS item scores (breathlessness, cough and sputum) were recorded in the daily diary card on a scale of 1 (no symptoms) to 5 (worst symptoms), with the BCSS total score being the sum of all three and ranging from 3 to 15. It was, however, noted that some patients recorded zero if they had no symptoms, rather than score 1 as defined in the original BCSS design. Therefore, in Study 2 (and subsequent clinical evaluations), symptoms were rated on a scale of 0 to 4, the BCSS total score consequently ranging from 0 to 12.

Assessment of lung function and rescue medication use

In both studies, PEF was recorded at home morning and evening, prior to the administration of study or rescue therapy. The number of actuations of rescue medication used was recorded daily.

Measurements of FEV_1, FVC and slow vital capacity (SVC) were determined at every study visit except follow-up and patients were asked not to use any bronchodilator medication, including the study medication, for 4 hours prior to spirometric assessments. Measurements were made, where possible, at the same time of day, using the same spirometer and a standard technique at each centre. SVC was measured before forced expiratory manoeuvres, and the best of three separate measurements was used. Three separate manoeuvres were also used to measure FEV_1 and FVC with the best one recorded.

In Study 2, a subset of patients with FEV_1 reversibility of 5 to 15% of baseline, were identified to determine the bronchodilator properties of sibenadet at the start and end of the treatment period. FEV_1 was recorded predose and at 5, 15, 30, 45, 60, 90, 120 minutes and hourly thereafter until 8 hours after dosing. Using the trapezoidal rule, bronchodilation was summarized as the area under the FEV_1 time curve from 0 to 8 hours (AUC_{0-8h} FEV_1), as litres per second over time.

Health-related quality of life (HRQL)

HRQL was assessed at the beginning and end of the treatment periods using the patient-completed St George's Respiratory Questionnaire (SGRQ) (19) in all countries except the Czech Republic, Hungary, and Poland, where linguistic validation of the SGRQ questionnaire had not been performed.

Safety measurements

Incidence and severity of adverse events were recorded throughout the two studies. Heart rate, blood pressure, electrocardiogram, and blood and urine samples for routine haematology, clinical chemistry, and urinalysis, were evaluated at the beginning and end of the treatment period in all patients.

Statistical analyses

In both studies, all patients who were randomized and received at least one dose of study medication were included in the Intent to Treat (ITT) and safety populations upon which the efficacy and safety analyses were respectively based. Patients were analysed according to the treatment they received. In both studies, the BCSS total scores for patients who discontinued prematurely from the study were imputed based on the mean of the BCSS total score on the last 3 days of treatment. Unless otherwise stated, all statistical testing was two-sided at the 5% significance level.

In Study 1, the changes in mean score from baseline in BCSS total and item scores were analysed for each of the weekly treatment periods and over the whole treatment period, using a non-parametric Mack–Skillings test (20). Pairwise median differences and adjusted 95% confidence intervals (CI) were calculated, based on the Wilcoxon Rank Sum test. This methodology was also used in the analysis of the SGRQ data. For lung function measurements (FEV_1 and FVC, measured in the clinic, and PEF assessments, recorded in the diary cards) an analysis of variance (ANOVA) model was used with treatment and country as fixed factors. The median number of actuations of rescue medication per day was analysed in the same way as BCSS total score. The primary comparisons (1000 μg sibenadet *vs.* placebo, salbutamol and IB) were made at the 1·7% significance level.

In Study 2, the changes from baseline in mean BCSS total and item scores were analysed for each 2-weekly treatment period and over the whole treatment period using ANCOVA with treatment and centre as fixed factors and mean baseline score as a covariate. The least squares (LS) means, SEs and corresponding 95% CIs were derived. Spirometric, PEF, rescue medication and SGRQ data were analysed using the same methodology.

It was planned to randomize 750 patients into Study 1 so that a minimum of 600 patients (100 per treatment group) would complete the study. This was based on results observed in the National Mucolytic survey (21) where a difference between treatments in global assessment of 0·92 with a SD of 2·968 was observed; 600 completed patients would allow a treatment difference of 1·37 in BCSS total score to be detected at the 1·7% level of significance with 80% power, using two-sided tests. Based on the results from Study 1, it was planned to randomize 865 patients into Study 2 so that a minimum of 720 patients (180 per treatment group) would complete the study. Assuming a SD of 1·46 this would allow the detection of a difference of 0·5 in the BCSS total score between sibenadet and placebo, using two-sided testing at the 5% significance level with 90% power.

RESULTS

Patient demographics

Patient disposition for studies 1 and 2 is summarized in Figure 1. In both studies, failure to complete was primarily due to adverse events, deterioration of patient condition, withdrawal of consent or a protocol deviation. Withdrawal rates were similar between the treatment groups and there were no obvious differences in the reasons for withdrawal. Patient demographics and baseline characteristics are outlined in Table 1. Any differences noted between treatment groups at baseline were deemed random and not considered to influence the endpoints of this study. Compliance with study therapy assessed from daily diary entries was over 90% in all treatment groups.

Efficacy of sibenadet in relieving key COPD symptoms

Data from Studies 1 and 2 were derived using different analytical approaches and the results of these analyses are therefore discussed separately throughout. The results of the proof of concept study (Study 1) demonstrated a reduction from baseline in mean daily BCSS total score over the 28-day treatment period in patients treated with sibenadet. When compared with placebo, this improvement was statistically significant with all doses of sibenadet, with the greatest reduction in total score seen with the 600 μg dose (Figure 2a). There were small reductions from baseline in mean BCSS total score with salbutamol and IB. The change from baseline in mean BCSS total score in the sibenadet 600 μg dose group was also greater than that in the salbutamol and IB groups (Figure 2b).

In study 2, the change from baseline in mean BCSS total score over the course of the study (weeks 1–2, 3–4 and 5–6) was seen to be dose-related, with the smallest change in the 45-μg group and the largest change in the sibenadet 495-μg group (Figure 3). The most marked

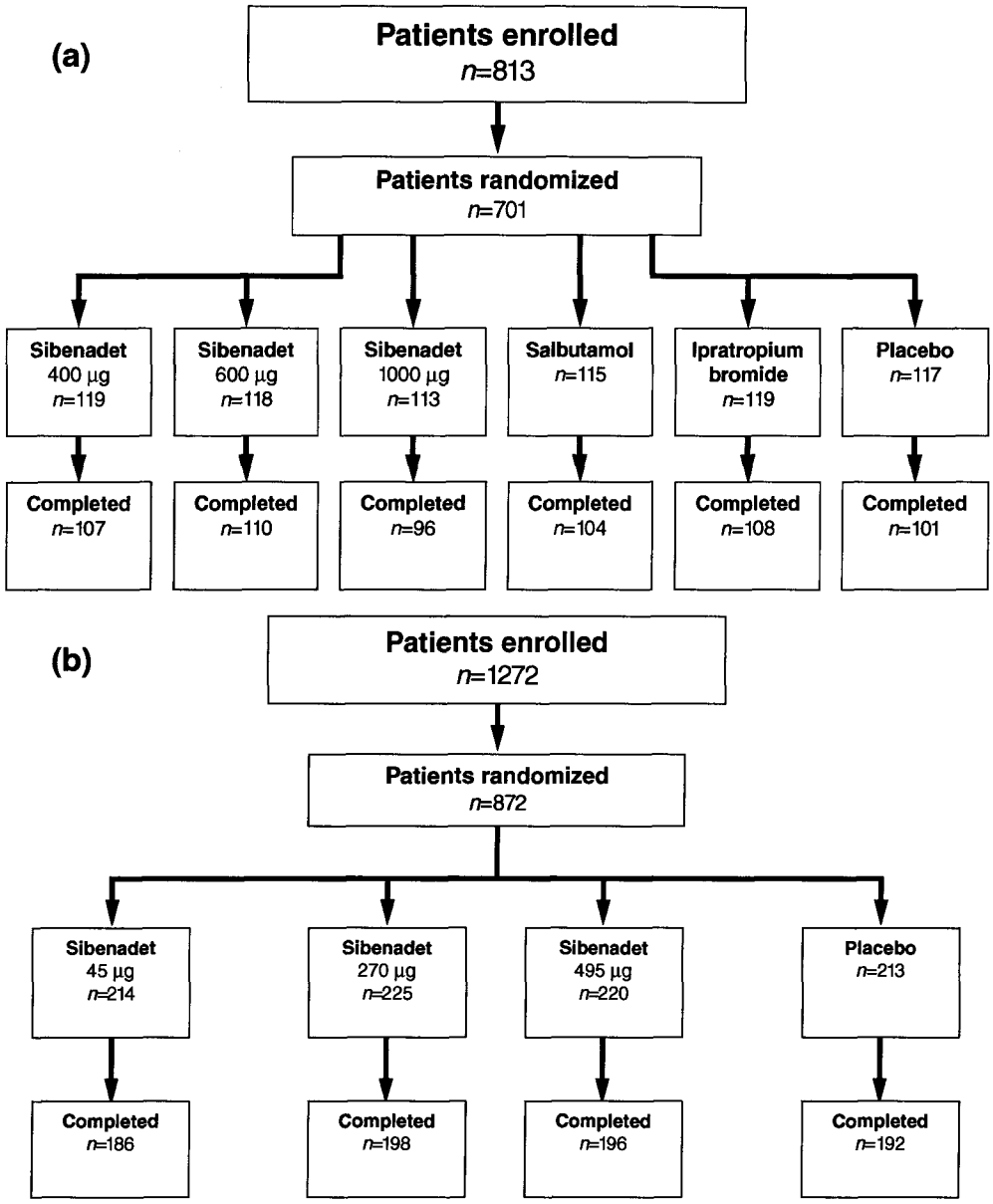

FIGURE 1. Patient disposition (a. Study 1; b. Study 2).

decreases were seen in the early weeks of the study. The LS mean changes from the baseline period to the full 6-week treatment period in mean daily BCSS total score were –0·22, –0·44 and –0·55 for the sibenadet 45, 270 and 495-µg groups respectively and –0·16 for the placebo group. The corresponding LS mean differences in these changes between placebo and each of the three sibenadet groups show that the two highest doses of sibenadet produced statistically significantly greater changes in mean daily BCSS than placebo (Figure 4).

BCSS item scores

In Study 1, the reduction between mean breathlessness scores over the baseline period and the treatment period was greater in the sibenadet groups than in the placebo group. The median differences from placebo and 95% CIs were 400 µg: –0·1 (–0·3, –0·1), 600 µg: –0·3 (–0·4, –0·2), 1000 µg: –0·2 (–0·3, –0·1). However, neither cough nor sputum item scores differed between treatments.

In Study 2, the dose response seen with the BCSS total scores was also reflected by the item scores. The mean daily Breathlessness scores decreased from baseline in all treatment groups, with the greatest effect seen in the first 2 weeks. Over the 6-week period, the LS mean differences (± SE) between the sibenadet (45, 270 and 495 µg) groups *vs.* placebo were –0·04 ± 0·05 (95% CI –0·14 to 0·06), –0·13 ± 0·05 (95% CI –0·23 to –0·03) and –0·14 ± 0·05 (95% CI –0·24 to –0·04) respectively.

Table 1. Summary of demographics and baseline characteristics

	Study 1 (Proof of Concept)						Study 2 (Dose-ranging)			
	Sibenadet (μg)			Salbutamol	IB	Placebo	Sibenadet (μg)			Placebo
	400	600	1000				45	270	495	
No. randomized	119	118	113	115	119	117	214	225	220	213
Sex: male/female	85/34	93/25	82/31	85/30	81/38	92/25	141/73	159/66	145/75	141/72
Mean age (years ± SD)	60 ± 7·6	61 ± 6·8	60 ± 6·7	60 ± 7·0	60 ± 6·6	60 ± 6·7	62 ± 7·4	64 ± 7·0	63 ± 7·5	62 ± 7·8
(Range)	(44–70)	(44–70)	(42–70)	(45–73)	(44–71)	(44–70)	(44–76)	(45–75)	(45–75)	(44–75)
Current smoker	45%	47%	46%	52%	45%	43%	42%	45%	45%	44%
Mean pack years (± SD)	41 ± 20·7	49 ± 32·7	42 ± 18·4	43 ± 22·3	43 ± 25·1	42 ± 19·1	45 ± 20·8	45 ± 22·4	45 ± 23·1	45 ± 22·3
Mean daily BCSS total score (± SD)*‡	7·0 ± 2·08	7·5 ±2·29	7·0 ± 2·22	7·2 ± 2·27	7·0 ± 1·95	6·9 ± 2·03	5·1 ± 2·06	5·3 ± 1·95	5·0 ± 1·86	5·0 ± 1·81
Mean percent predicted FEV_1 (± SD)†	45 ± 13·4	41 ± 12·4	42 ± 12·4	43 ± 12·4	43 ± 13·2	45 ± 12·7	43 ± 13·7	42 ± 12·8	42 ± 13·2	42 ± 12·6
Mean reversibility in FEV_1 (percent ± SD)	9 ± 12·0	13 ± 13·7	9 ± 14·0	11 ± 14·6	11 ± 12·4	10 ± 12·8	7 ± 8·4	8 ± 8·5	9 ± 8·5	8 ± 10·0
Mean morning PEF ($l\ min^{-1}$ ± SD)*	239 ± 92	225 ± 81	223 ± 76	241 ± 86	239 ± 86	242 ± 84	233 ± 89	228 ± 92	220 ± 83	228 ± 85

*Mean of the overall baseline period.
†Mean of assessment performed at first study visit.
‡Scale for total score Study 1 = 3–15, Study 2 = 0–12.

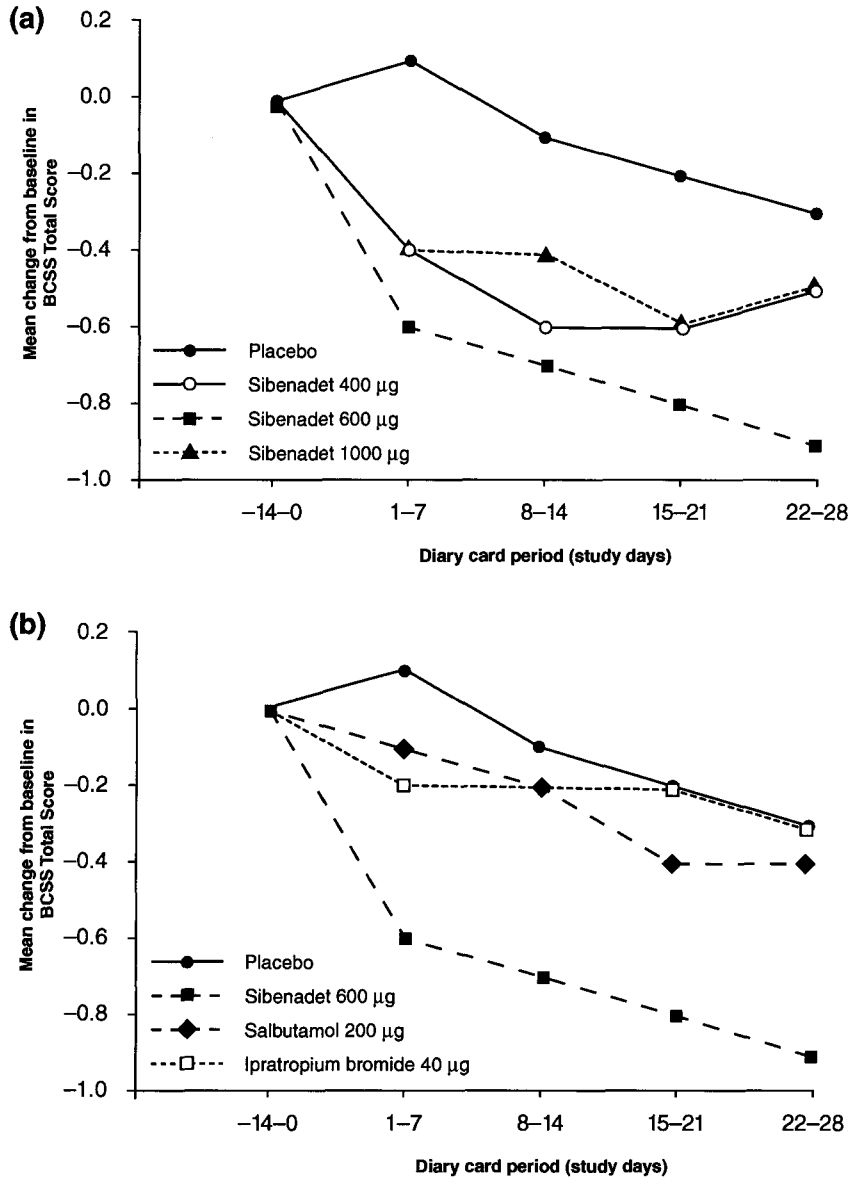

FIGURE 2. Mean changes in BCSS Total Score (days 1–28) from baseline: comparison of three sibenadet doses and placebo (sibenadet 400 µg *vs.* placebo P=0·015, sibenadet 600 µg *vs.* placebo $P < 0·001$, sibenadet 1000 µg *vs.* placebo P=0·009); comparison of sibenadet *vs.* salbutamol and IB (sibenadet 600 µg *vs.* placebo $P < 0·001$, IB 40 µg *vs.* placebo P=0·505, salbutamol 200 µg *vs.* placebo P=0·149).

Mean daily Cough scores decreased from baseline in all treatment groups. The LS mean difference (± SE) between the sibenadet (45, 270 and 495 µg) and placebo groups being −0·02 ± 0·06 (95% CI −0·12 to 0·09), −0·08 ± 0·05 (95% CI −0·19 to 0·03) and −0·13 ± 0·05 (95% CI −0·23, −0·02) respectively.

Mean daily Sputum scores decreased from baseline in the two higher dose sibenadet groups only and the sibenadet 45-µg group showed no differences from placebo. The LS mean difference (± SE) between the sibenadet 270 and 495-µg and placebo groups were, however, −0·06 ± 0·05 (95% CI −0·16 to 0·04) and −0·12 ± 0·05 (95% CI −0·22 to −0·02).

Assessment of lung function and rescue medication use

In comparison with placebo, all sibenadet treatment groups (in both studies) demonstrated increased morning and evening PEF values over the entire study period, compared with baseline. In Study 1, the increases in PEF values for all sibenadet groups were statistically significantly greater than increases seen in the placebo and IB groups, with a trend towards superiority for sibenadet when compared with salbutamol (data not shown). No statistically significant improvement in FEV_1 or FVC as measured at clinic visits were seen in any

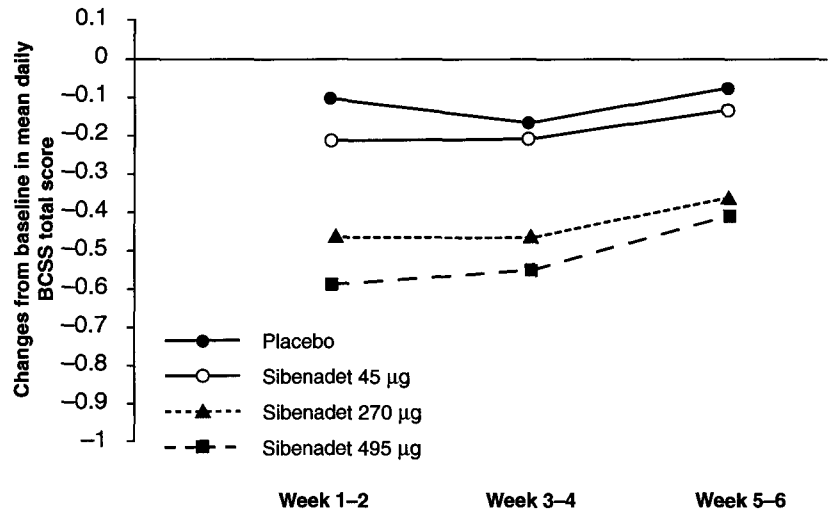

FIGURE 3. LS mean change from baseline in BCSS total score.

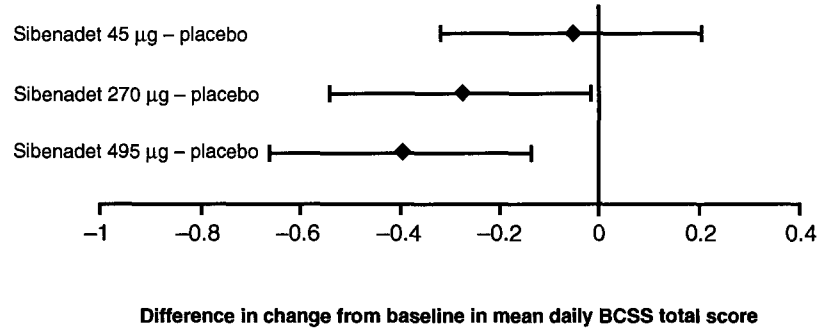

FIGURE 4. Plot of LS mean BCSS total scores and corresponding 95% confidence intervals; data show the difference between each sibenadet group and placebo in absolute changes from baseline over the full 6-week treatment period (data from Study 2).

group. In Study 2, the increases in PEF over the 6-week treatment period were statistically significant ($P < 0{\cdot}001$) compared with placebo for the 270 and 495 µg doses (Table 2). In addition, small increases in FEV_1, FVC and SVC were seen with all doses of sibenadet after 2 weeks' treatment and at the end of the treatment period (Table 2).

In Study 1, the use of rescue bronchodilator medication (measured as a mean value over the entire treatment period) was similar across the active treatment groups whilst more rescue medication was required in the placebo group. Mean (± SD) use of rescue medication over the 4-week treatment period in patients on active medication ranged from a minimum of 1·8 ± 2·97 actuations per day in the salbutamol group to a maximum of 2·2 ± 2·81 and 2·2 ± 3·18 actuations per day in the IB and sibenadet 600 µg groups, respectively. Rescue medication use in the placebo group was 3·1 ± 3·92 actuations per day.

In Study 2, rescue bronchodilator medication usage (measured as change in mean values over the entire treatment period compared with baseline values) was reduced in the sibenadet 270 and 495-µg groups with LS mean (± SE) reductions over placebo in both groups of 1·2 ± 0·27 puffs per day (95% CI −1·7 to −0·6 and −1·7 to −0·7 respectively).

Bronchodilator assessment

Serial FEV_1 measurements, performed in a subset of patients in Study 2, at the start and end of the 6-week treatment period, demonstrated bronchodilation in all sibenadet groups 5 minutes after dosing (the first measurement time point) (Figure 5). At the start of the treatment period for the first assessment, 104 patients were included, of whom 85 completed the full 8-h assessment (drop-out rates were 10, 12·5, 16 and 29% for the 45, 270, 495-µg sibenadet doses and placebo

Table 2. Outcome measures (mean ± SD) – change from baseline (spirometry, PEF, rescue medication usage – data from Study 2)

	Sibenadet			
	45 μg (*n*=214)	270 μg (*n*=225)	495 μg (*n*=220)	Placebo (*n*=213)
PEF (l min^{-1} ± SD)*				
Morning	*n*=212	*n*=224	*n*=219	*n*=212
	3·5 ± 24	14 ± 28	14 ± 26	0·1 ± 23
Evening	*n*=211	*n*=224	*n*=217	*n*=212
	6 ± 22	15 ± 28·5	15 ± 26	0 ± 23
Spirometry (l ± SD)†				
FEV_1	*n*=203	*n*=214	*n*=214	*n*=214
	0·02 ± 0·22	0·02 ± 0·23	0·03 ± 0·25	0·02 ± 0·27
FVC	*n*=203	*n*=214	*n*=214	*n*=204
	0·02 ± 0·43	0·02 ± 0·51	0·08 ± 0·45	0·02 ± 0·51
SVC	*n*=194	*n*=209	*n*=206	*n*=194
	0·00 ± 0·41	0·01 ± 0·48	0·06 ± 0·46	−0·03 ± 0·54
Rescue medication usage* (actuations day^{-1}, ± SD)	*n*=207 −1·0 ± 2·7	*n*=213 −1·8 ± 3·0	*n*=210 −1·8 ± 3·3	*n*=206 −0·5 ± 2·6

*Change over entire study period compared with baseline values.
†Change from baseline to last study visit.

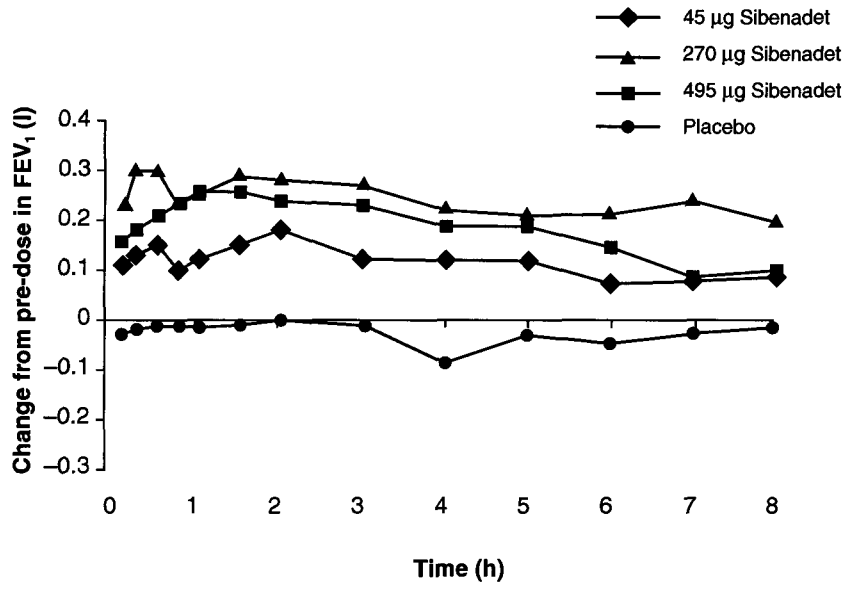

FIGURE 5. FEV_1 profile following a single dose of sibenadet 45, 270 or 495 μg (data from the start of the treatment period of Study 2).

respectively). The mean (± SD) maximum increases in FEV_1 for the 45, 270 and 495-μg sibenadet groups were 0·26 ± 0·18, 0·44 ± 0·40, and 0·33 ± 0·19 litres, respectively compared with 0·11 ± 0·13 litres with placebo. The time to reach maximum FEV_1 was similar in all sibenadet groups at approximately 2 hours after treatment.

At the end of the 6-week treatment period, 84 patients took part in the bronchodilator assessment, of whom 67 completed the full 8-h timecourse (drop-out rates were 15, 21, 23 and 14% for the 45, 270, 495-μg sibenadet doses and placebo respectively). The pattern of changes was similar to that seen at the start of the study period, although the changes in FEV_1 were less marked.

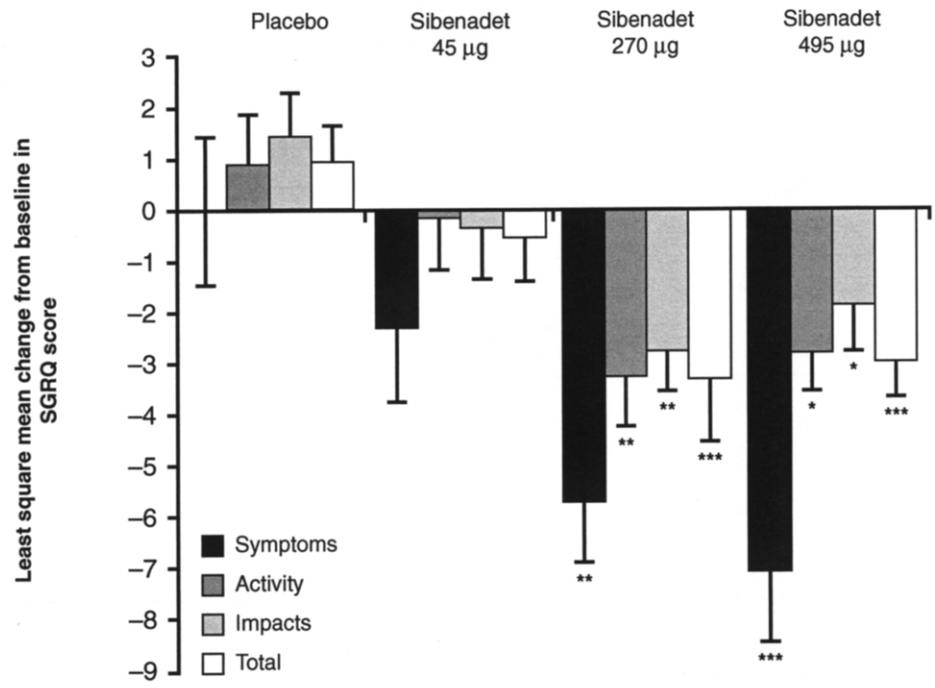

FIGURE 6. Least squares mean changes in three domains and Total score for SGRQ from baseline to the end of 6 weeks' treatment for sibenadet 45, 270 or 495 µg compared with placebo (bars indicate standard error). *P* values are for differences between sibenadet and 95% CIs for the difference between each of the sibenadet groups and placebo in mean BCSS total score in placebo. **P* < 0·05, ***P* < 0·005, ****P* < 0·001 (data from Study 2).

Health-related quality of life

In Study 1, SGRQ data were available for approximately 52% of patients due to the non-availability of linguistically validated questionnaires in some countries. For all the scores, the changes from baseline were generally small, with large standard deviations, reflecting variability in the data. There were median reductions of the overall score from baseline values in the groups receiving sibenadet 400 µg, or 1000 µg or salbutamol, no change in the sibenadet 600-µg group and small increases in the placebo and IB groups.

In Study 2, SGRQ data were available for approximately 85% of patients. At the end of the 6-week study period, the SGRQ overall score and each domain score had decreased for all three sibenadet dosage groups (Figure 6). For the 270 and 495-µg doses, these changes were statistically significant when compared with placebo.

Safety assessments

In both studies, no clinically relevant changes in mean laboratory values, vital signs or ECG variables were seen. Treatment emergent adverse events reported in Study 1 by ≥ 5% of patients in any group are summarized in Table 3. Treatment-emergent was defined as an event which was not present prior to administration of the first dose of study medication, but which became apparent after dosing, or a pre-existing event which worsened following dosing. There were no marked differences between the adverse event profiles of sibenadet, salbutamol or IB, except for the higher frequency of tremor in patients treated with sibenadet 1000 µg and taste of treatment at all doses of sibenadet. Eleven patients from the sibenadet 1000-µg group discontinued treatment due to one or more adverse events compared with five patients from the sibenadet 600-µg group. Of the 11 patients on the 1000-µg dose, seven discontinued treatment due to tachycardia and/or tremor. In the placebo group, ten patients discontinued treatment due to adverse events, nine of these withdrawals were due to worsening symptoms of COPD. There were three deaths during the study: one in the sibenadet 400-µg group following an exacerbation of COPD, one in the sibenadet 1000-µg group due to sepsis originating from pyelonephritis and one in the placebo group attributed to cardiac arrest. In total, 12 patients experienced non-fatal serious adverse events during or following study treatment. These included three on placebo, one on salbutamol, one on IB and three, three and four on sibenadet 400-µg, 600-µg and 1000-µg, respectively.

Study 2 also showed sibenadet to be generally well tolerated. The most commonly occurring adverse events that were reported more frequently at any sibenadet

Table 3. Summary of treatment emergent adverse events reported by ≥ 5% of patients in any group (data from Study 1)

	Sibenadet 400 μg n=119	Sibenadet 600 μg n=118	Sibenadet 1000 μg n=113	Salbutamol n=115	IB n=119	Placebo n=117
At least one event	60 (50%)	61 (52%)	66 (58%)	56 (49%)	54 (45%)	60 (51%)
General disorders						
Asthenia	7 (6%)	2 (2%)	2 (2%)	1 (1%)	2 (2%)	0 (0%)
Back pain	2 (2%)	6 (5%)	1 (1%)	1 (1%)	2 (2%)	1 (1%)
Chest pain	5 (4%)	3 (3%)	5 (4%)	4 (3%)	6 (5%)	4 (3%)
Fatigue	7 (6%)	2 (2%)	3 (3%)	4 (3%)	6 (5%)	2 (2%)
Central and peripheral nervous system disorders						
Dizziness	5 (5%)	4 (3%)	6 (5%)	4 (3%)	2 (2%)	2 (2%)
Headache	16 (13%)	9 (8%)	16 (14%)	9 (8%)	14 (12%)	14 (13%)
Tremor	4 (3%)	6 (5%)	23 (20%)	1 (1%)	3 (3%)	1 (1%)
Gastrointestinal system disorders						
Mouth dry	2 (2%)	1 (1%)	6 (5%)	3 (3%)	0 (0%)	0 (0%)
Nausea	5 (4%)	5 (4%)	7 (6%)	4 (3%)	5 (4%)	0 (0%)
Heart rate and rhythm disorders						
Tachycardia	0 (0%)	2 (2%)	7 (6%)	0 (0%)	0 (0%)	3 (3%)
Respiratory system disorders						
Coughing	10 (8%)	5 (4%)	2 (2%)	3 (3%)	5 (6%)	2 (2%)
Dyspnoea	14 (12%)	12 (10%)	10 (10%)	16 (14%)	10 (10%)	4 (12%)
Dyspnoea (aggravated)	5 (4%)	3 (3%)	5 (4%)	2 (2%)	4 (4%)	5 (7%)
Pharyngitis	2 (2%)	3 (3%)	2 (2%)	6 (5%)	3 (3%)	2 (2%)
Rhinitis	2 (2%)	2 (2%)	3 (3%)	2 (2%)	2 (2%)	6 (5%)
Other						
Discernible taste	6 (5%)	3 (3%)	6 (5%)	0 (0%)	1 (1%)	0 (0%)

dose than placebo were: back pain, tremor, nausea, bronchitis, dyspnoea and aggravated dyspnoea, respiratory infection and discernible taste of treatment. Respiratory system disorders were the most commonly reported category of adverse event, with the lowest frequency reported in the sibenadet 495-μg group (25%) and highest frequency in the 45-μg group (38%); reporting of respiratory events was 32% in the placebo group. Coughing, COPD and respiratory infection all occurred with lowest frequency on the sibenadet 495-μg dose, and with a lower frequency than on placebo. Twenty-three patients suffered non-fatal serious adverse events during the treatment period, six in the 45-μg group, six in the 270-μg group, seven in the 495-μg group, and four in the placebo group. The number of serious adverse events considered as possibly or probably related to study treatment was similar across the four treatment groups (sibenadet 45 μg and 270 μg: three; sibenadet 495 μg: four; placebo: two). During the treatment period, one patient in the placebo group died because of respiratory insufficiency. Three deaths occurred during the follow-up period (two attributed to myocardial infarction, one in the sibenadet 45-μg group and one in the 270-μg group; and one attributed to pneumonia in the 270-μg group). No deaths occurred in the highest dose sibenadet group. Ninety-one patients discontinued treatment either permanently or temporarily as a result of an adverse event during the treatment period, with a similar number in each group.

DISCUSSION

The hypothesis underlying the development of the novel D_2-receptor agonist effect of sibenadet is based on the knowledge that, breathlessness, cough and excessive mucus production, can all be mediated through stimulation of pulmonary sensory afferent nerves (11). Studies of animal models of COPD symptoms have demonstrated the efficacy of sibenadet in controlling such symptoms via its D_2 dopamine receptor agonist effect (16). The data from these *in vivo* studies indicate that dopaminergic agonists provide potentially therapeutic benefits, probably by acting on sensory nerves. In support of these findings, expression of D_2 dopamine receptors on the sensory neurones of thoracic dorsal root ganglia has recently been

demonstrated at the level of both mRNA and protein (22).

The results of the studies reported here provided clinical corroboration of the sibenadet hypothesis and preclinical findings. The initial proof of concept study was designed to determine the clinical potential of sibenadet therapy and indeed the dual D_2 dopamine, β_2-adrenoceptor agonist effect of sibenadet was seen to improve the key COPD symptoms of breathlessness, cough and sputum in this 28-day study. This study also piloted the BCSS and highlighted its potential for use in future studies. This novel instrument has subsequently undergone a rigorous evaluation process to demonstrate its reproducibility, reliability and validity, thereby confirming its value in symptom assessment (17,18). As a proof of concept trial, Study 1 was not intended to demonstrate dose-response and indeed, greatest efficacy was observed in the sibenadet 600-μg dose group, with statistically significant reduction in BCSS total and item scores. It is possible that the 1000-μg sibenadet dose was less well tolerated than the lower dose, with adverse effects resulting in the patient feeling generally less well, thereby masking any additional efficacy afforded by the higher dose. This dose was not used in further studies. In contrast to the observed efficacy of sibenadet, salbutamol and IB produced only limited symptomatic improvements. These findings were, however, viewed with caution as a potentially sub-optimal therapeutic regimen was adopted for both comparators (i.e. three times daily rather than four times daily), in order to simplify the study design. This was considered warranted as the primary objective of the study was not comparative. Currently available therapy does little to improve the characteristic symptoms of breathlessness, cough, and sputum associated with COPD. Comparison with these bronchodilators offered validation of D_2 effects of sibenadet and therefore proof of concept for future development of this potentially useful novel therapy.

The symptomatic improvement observed in Study 1 provided the impetus for undertaking a second study designed to determine the therapeutic dose for sibenadet. This objective was clearly achieved, as dose-related improvements in BCSS total and item scores with sibenadet therapy were observed. The highest dose (495 μg) achieved greatest efficacy without compromising safety and therefore a 500-μg dose, delivered in two equal fractions, was used in subsequent large-scale studies (23).

COPD is typically associated with significant impairment of HRQL. Patients will generally tolerate disease symptoms, tending to present to healthcare professionals only when they recognize a decline in their ability to perform everyday activities (8,23). Assessment of HRQL is therefore an important, clinically meaningful therapeutic outcome measure in COPD (25,26). It is important to note that, in Study 2, the symptomatic benefits of sibenadet therapy were accompanied by statistically significant improvements in SGRQ overall and all domain scores at the two higher doses. These results also indicate a clinically meaningful improvement over placebo (as defined by a change in total score of $> 4{\cdot}0$) (19). While the SGRQ was not specifically designed to detect short-term changes in HRQL there was cause for optimism as sibenadet therapy appeared to demonstrate a rapid, positive effect on HRQL. However, as the SGRQ was originally developed to detect differences in HRQL in patients with asthma over the course of a year, it is possible that the short-term improvements observed could be artefactual. Treatment-related improvements in HRQL seen in Study 1 were less clear than those obtained in Study 2, possibly due to the small number of patients from which SGRQ data were obtained and the shorter study period.

Although predictable effects mediated by β_2-adrenoceptor stimulation occurred more often with sibenadet, particularly at the highest dose in both studies, the overall frequency for reporting adverse events was low. The incidence of adverse events associated with D_2 agonists (such as nausea and vomiting) was low and similar to that reported in the bronchodilator groups, supporting the lack of centrally mediated D_2 effects with sibenadet use. While there was a relatively high incidence of discernible taste of treatment with sibenadet, no patient withdrew from the study because of this effect alone. The overall safety profile of sibenadet appeared to be acceptable and subsequent large-scale evaluation has demonstrated a similar safety profile with no additional safety concerns (23).

While these early clinical studies were extremely encouraging, it is possible, especially with the benefit of hindsight, to detect some early evidence of reduced sibenadet effect over time. In Study 2, the change from baseline in BCSS total score was seen to decrease in the first 2 weeks of the study, whereas by weeks 5–6 a return towards baseline values was seen. In the light of the results of the longer-term studies (23) these results could be interpreted as early indicators of the tachyphylaxis seen with increased treatment duration. These longer-term observations, however, were obviously not known at the time and the decision to progress to Phase III development was justifiable.

In conclusion, the results of the early sibenadet clinical evaluation reported here indicated that this novel combination of a D_2 dopamine receptor and β_2-adrenoceptor agonist had important clinical potential for the treatment of COPD. The positive effects of sibenadet on COPD symptoms, HRQL and lung function appeared to be dose-related. Although these data appeared encouraging, it was acknowledged that the true potential of sibenadet for the symptomatic relief of COPD could only be determined from large-scale, long-term clinical

investigation. These studies have now been completed and have shown that the early clinical benefit observed in the studies reported here was not sustained in studies of longer duration (23).

ACKNOWLEDGEMENTS

We would like to thank the study investigators for their assistance in the collection of these data and the AstraZeneca Viozan team for their ongoing support. We would also like to thank Ruth Tidey for her assistance in the preparation of this manuscript.

REFERENCES

1. American Thoracic Society. Standards for the diagnosis and care of patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 1995; **152**: S77–S120.
2. O'Byrne PM, Postma DS. The many faces of airway inflammation. Asthma and chronic obstructive pulmonary disease. Asthma Research Group. *Am J Respir Crit Care Med* 1999; **159**: S41–S63.
3. The World Health Report 1997 – conquering suffering, enriching humanity. World Health Organization, Geneva, 1997; 47.
4. Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; **349**: 1498–1504.
5. Lopez AD, Murray CC. The global burden of disease 1998–2020. *Nat Med* 1998; **4**: 1241–1243.
6. Sullivan D, Ramsey SD, Lee TA. The economic burden of COPD. *Chest* 2000; **117**(2 Suppl): 5S–9S.
7. Pauwels RA, Buist AS, Calverley PM, *et al.* Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: National Heart, Lung and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Am J Respir Crit Care Med* 2001; **163**: 1256–1276.
8. Van den Boom G, Rutten-van Mölken MPMH, Tirimanna PRS, van Schayck CP, Folgering H, van Weel C. Association between health-related quality of life and consultation for respiratory symptoms: results from the DIMCA programme. *Eur Respir J* 1998; **11**: 67–72.
9. Vestbo J., E. Prescott, and P. Lange, and the Copenhagen City Heart Study Group. Association of chronic mucus secretion with FEV_1 decline and chronic obstructive pulmonary disease morbidity. *Am J Respir Crit Care Med* 1996; **153**: 1530–1535.
10. Doherty MJ, Mister R, Pearson MG, Calverley PMA. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. *Thorax* 2000; **55**: 643–649.
11. Undem BJ, Riccio MM. Activation of airway afferent nerves. In: Barnes PJ, Grunstein MM, Leff AR, Woolcock AJ, eds. *Asthma*. Philadelphia: Lippincott-Raven, 1997: 1009–1025.
12. Missale C, Nash SR, Robinson SW, *et al.* Dopamine receptors: from structure to function. *Physiol Rev* 1998; **78**: 189–225.
13. Jackson DM, Simpson WT. The effect of dopamine on the rapidly adapting receptors in the dog lung. *Pulm Pharmacol Ther* 2000; **13**: 39–42.
14. Xie GX, Jones K, Peroutka SJ, Palmer PP. Detection of mRNAs and alternatively spliced transcripts of dopamine receptors in rat peripheral sensory and sympathetic ganglia. *Brain Res* 1998; **785**: 129–135.
15. Bonnert RV, Brown RC, Chapman D, *et al.* Dual D_2-receptor and $beta_2$-adrenoceptor agonists for the treatment of airway diseases. 1. Discovery and biological evaluation of some 7-(2-aminoethyl)-4-hydroxybenzothiazol-2(3H)-one analogues. *J Med Chem* 1998; **41**: 4915–4917.
16. Dougall IG, Young A, Ince F, Jackson DM. Dual dopamine D_2 receptor and β_2-adrenoceptor agonists for the treatment of COPD: the pre-clinical rationale. *Respir Med* 2003 (suppl).
17. Leidy NK, Schmier J, Jones MKC, Lloyd J, Rocchiccioli K. Evaluating symptoms in COPD: validation of the Breathlessness, Cough and Sputum Scale©. *Respir Med* 2003 (suppl).
18. Leidy NK, Rennard S, Schmier J, *et al.* The Breathlessness, Cough, and Sputum Scale (BCSS): empirically-based guidelines for interpretation. Submitted to *Chest*, 2002.
19. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med* 1991; **85**: Suppl B:25–31.
20. Mack GA, Skillings JH. A Friedman-type rank test for main effects in a two-factor ANOVA. *J Am Stat Assoc* 1990; **75**: 947–951.
21. Petty T. The National Mucolytic Study. Results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest* 1990; **97**: 75–83.
22. Trevisani M, Peiser C, Rigoni M, *et al.* D_2 receptors are expressed in rat dorsal root ganglion neurons and are inhibitory. *Eur Resp J* 2001; **18**; (suppl 33):242s.
23. Laursen LC, Lindqvist A, Hepburn T, *et al.* The role of the novel D_2/β_2-agonist, Viozan™ (sibenadet HCl), in the treatment of symptoms of COPD: results of a large-scale clinical investigation. *Respir Med* 2003 (suppl).
24. Curtis JR, Deyo RA, Hudson LD. Pulmonary rehabilitation in chronic respiratory insufficiency. 7. Health-related quality of life among patients with chronic obstructive pulmonary disease. *Thorax* 1994; **49**: 162–170.
25. Mahler DA. How should health-related quality of life be assessed in patients with COPD? *Chest* 2000; 117:**2** Suppl: 54S–57S.
26. Yusen RD. What outcomes should be measured in patients with COPD? *Chest* 2001; **119**: 327–328.